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A veterinary antiparasitic containing Avermectin/Ivermectin

[57] **Abstract:**

A veterinary antiparasitic of the present invention containing Avermectin (AVM) or Ivermectin (IVM), characterized in that it is made into a suspension concentrate, an emulsion, a cream containing 0.05-10% of AVM/IVM, and a composite formulation thereof mixed with levamisole, Albendazole and other parasiticides. The present invention contains veterinary antiparasitic containing AVM/IVM, which is low in production costs, simple in its production process, easy to use, and has good effects.

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Claims

1. A veterinary antiparasitic containing AVM/IVM, characterized in that it is prepared into a suspension concentrate, an emulsion, and a cream containing 0.05-10% of AVM/IVM.

2. The antiparasitic according to claim 1, characterized in that the suspension concentrate is formed by mixing AVM/IVM with a wetting agent, a suspending agent, an antifreeze, a preservative, and a disperse medium; and its composition contents (calculated with the suspension concentrate as 100%) are: 0.05-10% of AVM/IVM, 0.2-10% of the wetting agent, 0.2-30% of the suspending agent, 5-15% of the antifreeze, 0.1-1% of the preservative, and the balance is the disperse medium.

3. The antiparasitic according to claim 1, characterized in that the emulsion is formed by mixing with a organic solvent, an emulsifier, a tackifier, an antifreeze, a preservative and water, and its composition contents (calculated with the emulsion as 100%) are: 0.05-10% of AVM/IVM, 2-80% of the organic solvent, 1-30% of the emulsifier, 0.2-10% of the tackifier, 5-10% of the antifreeze, 0.1-1% of the preservative, and the balance is water.

4. The antiparasitic according to claim 1, characterized in that the cream is formed by mixing AVM/IVM with an organic solvent, an emulsifier, a tackifier, an antifreeze, a preservative and water, and its composition contents (calculated with the cream as 100%) are : 0.05-10% of AVM/IVM, 2-80% of the organic solvent, 1-30% of the emulsifier, 0.5-30% of the tackifier, 5-10% of the antifreeze, 0.1-1% of the preservative, and the

balance is water.

5. The antiparasitic according to claims 2 and 4, characterized in that said wetting agent comprises Tween-80, sodium dodecyl sulfate and sodium dodecyl benzenesulfonate; said suspending agent comprises xanthan, gum arabic, methylcellulose and carboxymethyl cellulose; said antifreeze comprises ethylene glycol, propylene glycol and glycerol; said emulsifier comprises Tween-80, OP-10 and OP-21; said preservative comprises sodium benzoate, sodium salicylate and phenylmethanol; said organic solvent comprises ethanol, acetone and acetic ether; and said disperse medium comprises water, animal fat and vegetable oil.

6. A composite formulation of veterinary antiparasitic containing AVM/IVM, characterized in that the single agent of said suspension concentrate, emulsion, and cream containing AVM/IVM according to claims 1 to 4 is formulated by mixing with a parasiticide comprising levamisole and Albendazole, so as to prepare a composite formulation suspension concentrate, a composite formulation emulsion, or a composite formulation cream, and the amount of said parasiticide added is 1-20% of the total composite formulation weight.

Description

A veterinary antiparasitic containing Avermectin/Ivermectin

The present invention belongs to a veterinary antiparasitic, and more specifically, the present invention is a veterinary antiparasitic suspension concentrate, emulsion, and cream of Avermectin B₁ (AVM for short) or its derivate Ivermectin (IVM for short).

In the 1980s, American company MERK had successfully developed AVM or IVM as veterinary antiparasitics, but at present they both have the dosage forms of powder, injection, capsule and liniment, and all these dosage forms have some disadvantages, such as there is dust pollution in the production of the powder, which affects the health of the operators, the liniment needs to be used in large doses, and the powder, capsule and injection dosage forms are not convenient for administration.

An object of the present invention is to overcome some of the disadvantages in the prior art, and to provide a veterinary antiparasitic suspension concentrate, emulsion, and cream containing IVM or AVM, which is of low production costs and high pharmacodynamic action.

Said suspension concentrate in the present invention is composed of AVM, a wetting agent, a suspending agent, an antifreeze, a preservative, and a disperse medium, and its composition contents (calculated with suspension concentrate as 100%) are: 0.5-10% of IVM or AVM, 0.2-10% of the wetting agent,

0.2-30% of the suspending agent, 5-15% of the antifreeze, 0.1-1% of the preservative, and the balance is the disperse medium.

The process for preparing said suspension concentrate is by using a common preparation technology, i.e. mixing AVM or IVM with the wetting agent and the disperse medium, after having homogenized and ground the mixture to 20-80 micron with a colloid mill, and then grinding it into 0.25 micron with a bead mill, adding the suspending agent, antifreeze and preservative, and homogenizing the same with a high speed shearing and emulsifying disperser, so as to obtain the suspension concentrate.

The composition and contents of said emulsion in the present invention (calculated with emulsion as 100%) are: 0.05-10% of AVM/IVM, 2-80% of the organic solvent, 1-30% of the emulsifier, 0.2-10% of the tackifier, 5-10% of the antifreeze, and 0.1-1% of the preservative, and the balance is water.

The preparation process for said emulsion is by using a common preparation technology, i.e. dissolving AVM or IVM with an organic solvent, adding the emulsifier, mixing them uniformly, adding a stabilizer, antifreeze and water, and homogenizing the mixture with a high speed shearing disperser, so as to obtain the emulsion.

The composition and contents of said cream in the present invention (calculated with the cream as 100%) are: 0.05-10% of AVM/IVM, 2-80% of the organic solvent, 1-30% of the emulsifier, 0.5-30% of the tackifier, 5-10% of the antifreeze, and 0.1-1% of the preservative, and the balance is water.

The preparation process for said cream is the same as that for the emulsion, only more tackifier is added therein to make it into a paste or cream which does not flow easily.

Said AVM in the present invention is the metabolic product of *Streptomyces avermitilis*, which is composed of eight structures i.e. the homolog of A_{1a}, A_{1b}, A_{2a}, A_{2b}, B_{1a}, B_{1b}, B_{2a}, and B_{2b}, in which the component B_{1a} has the highest parasitocidal activity and the widest parasitocidal spectrum, but the structures of the B_{1b} and B_{1a} are too similar to separate them, so it is often the mixture of the two which is abbreviated as AVM, and said IVM (Ivermectin) is a derivate of the AVM (William C. Campbell, "Ivermectin and Abamectin", Springer-verlag New York Inc, 1989, P1-23).

Said AVM or IVM can also be made into an oily liquid to replace the crystal products of AVM or IVM with a purity of about 90% (or called AVM or IVM technical). The process for preparing the oily liquid is: the bacteria strain for production is fermented for 7-9 days and filtered to obtain the hyphostroma, after the hyphostroma has been lixiviated with acetone, ethanol or other organic solvents and filtered, the lixiviation liquid is recovered decolorized and having toxic components removed, it is concentrated into an oily paste form under a reduced pressure, and this paste mixture contains 3-10% of Avermectin A₁, 8-25% of A₂, 6-25% of B₁, 3-10% of B₂, 10-30% of lipides and 5-10% of water.

Said wetting agent comprises Tween-80, sodium dodecyl sulfate, sodium dodecyl benzenesulfonate; said suspending agent comprises xanthan, gum arabic, methylcellulose and

carboxymethylcellulose; said antifreeze comprises ethylene glycol, propylene glycol; said emulsifier comprises Tween-80, OP-10 and OP-21; said preservative comprises sodium benzoate, sodium salicylate, and phenylmethanol; said organic solvent comprises acetic ether, acetone and ethanol; and said disperse medium comprises water, animal fats and vegetable oils.

Other known parasiticides can be added into the single agent of the abovementioned suspension concentrate, emulsion, and cream to prepare a composite formulation suspension concentrate, a composite formulation emulsion, and a composite formulation cream. Said other parasiticides comprise levamisole and Albendazole, the amount added is 1-20% of the composite formulation weight, and the way to add them is by mixing the other components into the single agent during its preparation or by adding them into the single agent already prepared and then mixing them uniformly.

The suspension concentrate, emulsion, and cream or their composite formulation of the present invention can be used in cattle, goat and sheep for expelling parasites, comprising nematodes in vivo and parasites in vitro, such as acari, tick, lice, fly larvae, etc. When the composite formulations of the suspension concentrate, emulsion, and cream are used in doses, they are diluted with water and they are administered orally with a dosage calculated according to 0.2 mg of AVM (or IVM) per kg body weight.

The veterinary antiparasitic preparation containing AVM or IVM as proposed in the present invention overcomes the disadvantages of the existing antiparasitic preparations; since

there is little or no organic solvent used, the production costs are reduced and the production process is simple, there is no dust pollution during production, its packaging is simple and convenient for use and it has good effects.

The features of the present invention are further described below with reference to examples:

Example 1

In this example, a suspension concentrate containing 0.1% of AVM was prepared.

0.55Kg of AVM technical (purity of 90%) was ground to less than 300 micron, and mixed with 1kg of sodium dodecyl sulfate and 2kg of water, then they were ground into 20-80 micron by a colloid mill and then further into 0.2-5 micron by a bead mill, then a solution of 1% carboxymethyl cellulose, 5% propylene glycol and 1% sodium benzoate was added to make up a total volume of 500L, which was homogenized to obtain the required suspension concentrate.

Example 2

In this example, a suspension concentrate containing 0.2% of AVM was prepared by using an oily liquid thereof.

2kg of an oily liquid containing 10% AVM was taken and added to 4L of Tween-80 and they were homogenized with a high speed shearing mixing and emulsifying machine at 50°C for homogenization, then after 10L of 1,2-propylene glycol had been added and mixed, a liquid of 0.3% xanthan was added to 100L, and the same was ground

to the solid particle size of less than 0.2 micron in a bead mill and it was ready.

Example 3

In this example, a suspension concentrate containing 10% of AVM was prepared.

55kg of AVM technical (purity of 90%) was ground to less than 300 micron, and mixed with 40kg of Tween-80 and 100kg of distilled water, then they were ground to about 20-80 micron by a colloid mill, then further ground to 0.2-5 micron with a bead mill, then 75kg of 1,2-propylene glycol and 0.5kg of sodium benzoate were added, and finally a liquid of 10% carboxymethyl cellulose was added to a total volume of 500L.

Example 4

In this example, an emulsion containing 0.2% of AVM was prepared. 1.1kg of AVM of 90% purity was dissolved with 10L of acetone, then 20L of Tween-80 was added, and they were mixed under high speed shearing to be homogenized, then a stabilizing liquid (containing 8% of methyl cellulose, 15% of 1,2-propylene glycol, 1% of phenylmethanol and the balance being water) was added to 500L, which was homogenized to obtain the emulsion.

Example 5

In this example, an emulsion containing 10% of AVM was prepared. The preparation procedure is the same as in example 3. Contents of the components are: 11kg of AVM (with a content of 90%), 11

kg of ethanol in 50L, 30L of Tween-80, and a stabilizing liquid (containing 0.2% of xanthan, 5% of 1,2- propylene glycol, 0.2% of sodium benzoate and the balance being water) was added to 100L, which was homogenized to obtain the emulsion.

Example 6

In this example, a cream containing 0.2% of AVM was prepared. 1.1Kg of AVM of 90% purity was dissolved with 10L of acetic ether and added to 10L of OP-10, and they were homogenized by an emulsion machine, then 75L of 1,2-propylene glycol, 1Kg of sodium salicylate were added, then a solution of 1% of gum arabic was added to 500L, which was homogenized to obtain the cream required.

Example 7

In this example, a cream containing 10% of IVM was prepared. The preparation procedure is the same as in example 5. Contents of the components are: 11Kg of IVM of a purity of 90%, 60L of acetone, 20L of Tween-80, 5L of 1,2-propylene glycol were homogenized, then a tackifier (containing 0.9% of xanthan, 0.2% of sodium benzoate, and the balance being water) was added to 100L, and finally it was homogenized to obtain the cream required.

Example 8

In this example, a composite formulation suspension concentrate containing 0.2% of AVM and 6% of Albendazole was prepared. 0.22kg of AVM of a purity of 90% was taken and added with 6kg of Albendazole, 5L of 1,2-propylene glycol, 1Kg of sodium benzoate

and 2L of Tween-80, they were ground to 0.2-5 micron in a bead mill and then a solution of 0.15% xanthan was added to 100L, and after a further grinding to homogenization it was ready.

Example 9

In this example, a composite formulation cream containing 5% of IVM and 18% of levamisole was prepared.

5.5Kg of IVM of a purity of 90% was taken and dissolved with 10L of ethanol, 5L Tween-80 was added, after they were mixed uniformly, 18kg of levamisole, 5L of 1,2-propylene glycol were added and mixed, then they were ground to the solid particle size of 0.2-4 micron and then added to 55.5L of a solution of 0.6% xanthan, 1L of 10% sodium benzoate solution and after they were stirred and sheared to homogenization, the composite formulation emulsion was ready.

Example 10

In this example, a composite formulation cream containing 5% of AVM and 18% of Albendazole was prepared by using an AVM oily liquid.

20kg of an oily liquid with a AVM content of 25% was taken, and 18kg of Albendazole, 20L of Tween-80, 5L of 1,2-propylene glycol were added, then they were ground to the solid particle size of 0.2-2 micron in a bead mill and added to 0.8% of xanthan to 100L, which was further ground to homogenization to obtain the required product.

Example 11

This example is the comparison of the preparations of this invention with AVM powder and capsules. The results are shown in Table 1 and Table 2.

Table 1 Table of comparison in the reduction rates of various nematode ova (larvae) in sheep by different dosage forms of AVM

Dosage form	Dosage (mg/Kg)	ova (larvae) reduce rate				
		Trichostrongylus	Ostertagia	Nematodirus	Dictyocaulus (larvae)	Protostrongylus (larvae)
Example 2 suspension concentrate	0.2	100	98.7	100	100	95.0
Example 4 emulsion	0.2	100	98.5	100	100	93.5
Example 6 cream	0.2	100	98.5	100	100	93.7
0.2% AVM injection*	0.2	100	98.3	100	100	93.5
AVM powder**	0.2	98.5	97.7	100	98.2	90.3
AVM capsules***	0.2	97.6	97.2	100	98.0	89.5

*AVM injection was under the veterinary drug certificate No. 23 of Ref. xin-shou-yao-zheng-zi (94), Ministry of Agriculture of the People's Republic of China;

**VM powder was under the veterinary drug certificate No. 24 of Ref. xin-shou-yao-zheng-zi (94), Ministry of Agriculture of the People's Republic of China;

***AVM capsule was prepared in house, and the formulation was: 0.2% of AVM and the balance was CaCO_3 .

Table 2 Comparison of parasitocidal rates of in vivo parasites in sheep by the composite formulation suspension concentrate in example 8 and the single agents of AVM and Albendazole

items	Composite formulation	Albendazole Single agent	AVM single agent
AVM (mg/kg)	0.2	-	0.2
Albendazole (mg/kg)	6	6	-
Trichostrongylus	100	98.3	98.7
Ostertagia	100	97.6	99.2
Marshallagia	98.7	98.0	98.3
Nematodirus	100	100	100
Oesophagostomum	100	97.2	98.0
Dictyocaulus	99.2	98.5	99.2
Moniezia (imago)	100	100	0
Avitellina	100	97.3	0